REMARKS

Status Summary

Claims 1-18 are pending in the application. Claim 7 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking adequate written description of the invention. Claims 1-12 and 14-17 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 1, 2, 4, 6-9, and 11-17 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Maloney. Claims 1-4, 7, and 11-17 are rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Ford. Claims 1-7 and 9-18 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ford. Claims 1, 2, 4-9, and 11-18 are newly rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Maloney. Claims 1-4, 7, 8, and 11-17 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ford in view of U.S. Patent No. 5,677,171 to Hudziak et al. (Hudziak). Claims 1, 2, 4, 6-8, and 11-17 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Maloney in view of Hudziak.

The specification is amended to correct typographical errors. Claims 1, 7, 9, 12, 14, and 17 are amended. New claims 19-27 are added. Reconsideration is respectfully requested in view of the amendments and following remarks.

Amendments to the Specification

The specification is amended to correct typographical errors, including clarification of dosage units used to describe an amount of anti-CD20 antibody to be administered. The dosage units are correctly stated as mg/m^2, as indicated in the specification as originally filed, including at page 11, line 1. The specification is also amended to provide the complete and correct reference citation at page 12, line 10.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claim 7 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking adequate written description of the invention on the basis that there is insufficient evidence that the RITUXAN® (rituximab) is publicly available. Official action, page 4, item 10. This rejection is respectfully traversed.

Initially, applicants respond that deposit of the antibody is not required to satisfy the written description requirement based on the disclosure of the complete sequence of the rituximab antibody in U.S. Patent No. 5,736,137. In particular, the examiner's attention is

directed to Figures 3A-3F, wherein the tandem chimeric antibody expression vector further comprising murine light and heavy chain variable regions is disclosed, which sequence corresponds to anti-CD20 in TCAE 8. Using the disclosed sequence, a skilled artisan could readily prepare the rituximab antibody.

In addition, cells expressing the RITUXAN® (rituximab) antibody are publicly available as deposit number 69119 from the American Type Culture Collection (ATCC). In support thereof, a statement issued by the ATCC, which confirms public availability of deposit number 69119, is submitted herewith.

Based on the foregoing, the subject matter of claim 7 is believed to be adequately described as required by 35 U.S.C. § 112, first paragraph. Therefore, applicants respectfully request that this rejection be withdrawn.

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 1-17 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite with respect to the phrase "high numbers" as used to describe an amount of circulating tumor cells in claims 1, 12, and 14. Official action, page 5, item 11. This rejection is respectfully traversed.

To more particularly claim the invention, claims 1, 12, and 14 are amended to specify that a subject treatable by the disclosed methods has a hematologic malignancy associated with at least about 40 X 10^9 white blood cells per liter. Support for the amendment can be found in the application as originally filed, including at pages 12-13 (Example 3), wherein it is described that median white blood cell counts of patients treated was 40 X 10^9/L (range 4-200).

Based on the foregoing, claims 1, 12, and 14 are believed to clearly describe the invention in accordance with 35 U.S.C. § 112, second paragraph, and withdrawal of the rejection of claims 1, 12, and 14 is respectfully requested.

In addition, claim 9 is amended to clarify dosage units as mg/m^2. Support for the amendment as originally filed is found throughout the specification, including at page 11, line 1. Claims 7 and 17 are amended to include the generic term "rituximab" as used to describe the trade name RITUXAN®.

Rejection of Claims Under 35 U.S.C. § 102(b)

Claims 1, 2, 4, 6-9, and 11-17 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Maloney et al. (1997) *Blood* 90(6):2188-2195 (Maloney). The examiner contends that Maloney describes administration of rituximab in an amount and dosage regimen sufficient to achieve a reduction in circulating tumor cells. Official action, pages 5-6, item 12. This rejection is respectfully traversed.

The study of Maloney excluded patients having CLL or those patients with high numbers of circulating lymphocytes, *i.e.*, greater than 5000 lymphocytes per microliter (*see* page 2193, column 2, lines 41-44). As noted herein above, claims 1, 12, and 14 are amended to specify that a subject treatable by the disclosed methods has a hematologic malignancy associated with at least about 40 X 10^9 white blood cells per liter. Therefore, Maloney fails to anticipate claims 1, 12, and 14 in lacking the element of treating a subject having a hematologic malignancy associated with circulating lymphocytes at the specified levels.

Maloney also fails to anticipate claim 13, which is directed to treatment of CLL, B-PLL, and transformed non-Hodgkin's lymphoma, which patients were not included in the Maloney study. Specifically, the study of Maloney is limited to patients with low-grade or follicular lymphoma. *See* page 2189, column 1, lines 19-21.

Claims 2, 4, 6-9, and 11 ultimately depend from claim 1, and claims 15-17 depend from claim 14. Thus, claims 2, 4, 6-9, 11, and 15-17 also include the element of treating a subject having a hematologic malignancy associated with at least about 40 X 10^9 white blood cells per liter, and Maloney also fails to anticipate these claims.

Based on the foregoing, claims 1, 2, 4, 6-9, and 11-17 are not anticipated by Maloney, and applicants request that the rejection of claims under § 102(b) based on Maloney be withdrawn.

Rejection of Claims Under 35 U.S.C. § 102(a)

Claims 1-4, 7, and 11-17 are rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Ford et al. (1998) *Highlights in Oncology Practice* 16(2):40-50 (Ford). Specifically, the examiner states that Ford describes administration of rituximab in combination with CHOP chemotherapy for the treatment of hematologic malignancies, including CLL. In the view of the examiner, "it is reasonable to conclude that with the

administration of the rituximab the method of avoiding or reducing the toxicity associated would occur simultaneously." Official action, pages 6-7, item 13.

Initially, applicants respond that the examiner's rationale for rejection is not clearly stated. Notwithstanding this ambiguity, applicants further respond that Ford fails to describe (1) administration of a therapeutically effective amount of an anti-CD20 antibody, and (2) reduction of circulating tumor cells. The examiner points to page 44, column 2, wherein it is stated that 3 of 4 patients having the highest level of circulating CD20+ cells showed a severe reaction to administration of rituximab, including infusion-related toxicity. The examiner also points to page 47, end of bridging paragraph, where it is stated that one CLL patient received rituximab therapy, who also showed severe infusion-related toxicity. Thus, the text referenced by the examiner does not support that administration of rituximab was therapeutic or resulted in a reduction of circulating tumor cells, as in claims 1-4, 7, and 11-17.

In addition, the examiner has not presented any evidence to support the notion that administration of rituximab to patients having high levels of circulating tumor cells would naturally be therapeutic. Contrary to this suggestion, the correlation between high levels of circulating CD20+ cells and the severity of adverse effects, as described by Ford, clearly demonstrates otherwise.

Given that every element of the claimed methods is not described by Ford, either expressly or inherently, Ford does not anticipate the present invention. Based thereon, withdrawal of the rejection of claims 1-4, 7, and 11-17 under § 102(a) based on Ford is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 103(a)
Based on Ford

Claims 1-7 and 9-18 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ford. The examiner acknowledges that Ford does not teach administration of rituximab at the specific dosages and time points set forth in claims 5, 9, and 18. Despite this deficiency, the examiner contends that a skilled artisan would have been motivated to optimize dosage with a reasonable chance of success. Official action, page 7, item 14. This rejection is respectfully traversed.

The examiner bears the burden of presenting a *prima facie* case for obviousness, with a showing of such *prima facie* obviousness requiring: (1) some suggestion or motivation,

either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined references; and (3) a reasonable expectation of success. MPEP § 2143.

The examiner has not established a *prima facie* case of obviousness. Initially, applicants respond that the examiner's stated rationale for rejection of claims is limited to alleged obviousness of administering rituximab at the dosages and regimens in claims 5, 9, and 18. Thus, the rejection should also be limited to claims 5, 9, and 18.

As noted herein above, Ford does not anticipate the present invention in failing to disclose the claimed elements of (1) administration of a therapeutically effective amount of an anti-CD20 antibody, and (2) reduction of circulating tumor cells. In addition, a reasonable chance of success in treating hematologic malignancies characterized by high numbers of circulating tumor cells was lacking prior to the disclosure of the present application. In particular, Ford teaches against such success, describing a correlation between high levels of circulating CD20+ cells and the severity of adverse effects of immunotherapy. Any perceived obviousness with respect to optimizing dosage and administration regimen does not cure these deficiencies.

In addition, applicants assert that tumor cells in patients having a hematologic malignancy associated with high levels of circulating tumor cells do not express CD20 antigen at the high densities characteristic of low grade B cell lymphomas. Thus, it could not have reasonably been predicted that the CD20 antigen would constitute an appropriate target for immunotherapy of such malignancies.

Based on the foregoing, claims 1-7 and 9-18 are believed to be non-obvious over the disclosure of Ford, and withdrawal of the rejection of claims under § 103(a) based on Ford is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 103(a)

Based on Maloney

Claims 1, 2, 4-9, and 11-18 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Maloney. Similar to the rejection under § 103(a) based on Ford, the examiner contends that Maloney is anticipatory except to the extent that claims 5, 9, and 18

are directed to particular dosages for rituximab administration. Official Action, pages 7-8, item 15. This rejection is respectfully traversed.

As in the foregoing rejection of claims under § 103(a), the examiner's rationale for rejection is relevant only to claims 5, 9, and 18, and therefore, applicants respond that the rejection of claims should also be so limited.

Notwithstanding the unsupported breadth of the rejection, applicants further respond that claims 1, 12, and 14 are amended to specify treatment of a subject having a hematologic malignancy associated with at least about 40 X 10^9 white blood cells per liter. As noted above in response to the rejection of claims under § 102(b), Maloney fails to anticipate the claimed methods because patients having the specified high levels of circulating tumor cells were expressly excluded from the study.

Maloney also fails to suggest or motivate treatment of such patients. Even if a suggestion or motivation to perform the claimed methods could be found in Maloney, a reasonable chance of success is lacking. In particular, Ford teaches against such success, as noted above. Any perceived obviousness with respect to optimizing dosage and administration regimen does not cure this deficiency.

Thus, the examiner has failed to make a *prima facie* case of obviousness based on Maloney, and applicants respectfully request withdrawal of the rejection of claims 1, 2, 4-9, and 11-18 under § 103(a) based on this document.

Rejection of Claims Under 35 U.S.C. § 103(a)
Based on Ford and Hudziak

Claims 1-4, 7, 8, and 11-17 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ford in view of U.S. Patent No. 5,677,171 to Hudziak et al. (Hudziak). The examiner relies on Hudziak as teaching administration of a lymphokine such as TNFα. The examiner contends that, given the known role of TNFα in suppressing cell growth and inducing cytotoxicity of tumor cells, it would have been obvious to administer TNFα in combination with anti-CD20 antibodies, and that upregulation of CD20 on the surface of tumor cells, as used in the present invention, is intrinsic to this administration. Official action, pages 8-9, item 16. This rejection is respectfully traversed.

As noted above, the claimed methods are not rendered obvious by Ford, which in fact teaches away from treatment of patients having the specified high levels of circulating tumor

cells (*i.e.*, at least about 40 X 10^9 white blood cells per liter) so as to produce a reduction in circulating tumor cells, as presently claimed. The deficiency of Ford is not cured by Hudziak, which teaches use of anti-HER2 antibodies for sensitization of tumor cells to subsequent treatment with TNF-α. Hudziak does not describe treatment of patients having a hematologic malignancy so as to reduce high levels of circulating tumor cells. Thus, the combined teachings of Ford and Hudziak do not render obvious the claimed invention.

Based on the foregoing, applicants respectfully request withdrawal of the rejection of claims 1, 2, 4, 6-8, and 11-17 under § 103(a) based on Maloney and Hudziak.

Rejection of Claims Under 35 U.S.C. § 103(a)
Based on Maloney and Hudziak

Claims 1, 2, 4, 6-8, and 11-17 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Maloney in view of Hudziak. The basis for this rejection is essentially that set forth with respect to Ford in view of Hudziak. Official action, pages, 9-10, item 17. This rejection is respectfully traversed.

As noted above, the claimed methods are not rendered obvious by the Maloney, which fails to describe, suggest, or motivate treatment of patients having the specified high levels of circulating tumor cells (*i.e.*, at least about 40 X 10^9 white blood cells per liter), as presently claimed. The deficiency of Maloney is not cured by Hudziak, which teaches use of anti-HER2 antibodies for sensitization of tumor cells to subsequent treatment with TNF-α. Specifically, Hudziak does not describe treatment of patients having a hematologic malignancy, and in particular a hematologic malignancy characterized by high levels of circulating tumor cells. Thus, the combined teachings of Maloney and Hudziak do not render obvious the claimed invention.

Based on the foregoing, applicants respectfully request withdrawal of the rejection of claims 1, 2, 4, 6-8, and 11-17 under § 103(a) based on Maloney and Hudziak.

Discussion of New Claims

New claims 19-27 are added to more particularly describe hematologic malignancies treatable by the claimed methods. Support for the claims can be found in the application as originally filed at page 9, lines 12-13, wherein mean pretreatment levels of circulating tumor cells are identified as 98 X 10^9 cells per liter (range 73-132), and at pages 12-13, bridging

sentence, wherein mean pretreatment levels of circulating tumor cells are identified as 40 X 10^9 cells per liter (range 4-200). Entry of the new claims is requested.

Conclusion

All objections and rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, she is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,
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January 29, 2004

TAC/JBM